MEDICAL PROGRESS

THE Rh FACTOR IN CLINICAL OBSTETRICS

E. W. OVERSTREET, M.D., H. F. TRAUT, M.D., M. L. HUNT, M.A., AND S. P. LUCIA, M.D.**,
San Francisco

OBSTETRICIANS have recognized with extraordinary rapidity the practical importance of the recently-gained knowledge concerning the Rh blood factor. Since its discovery by Landsteiner and Wiener[5] in 1940, the clinical implications of its behavior have been accorded widespread consideration and use. Indeed, the mechanism of action of the Rh factor both in transfusion reactions and during gestation is now such common knowledge, thanks to numerous comprehensive review papers,[2,3,11,14,15] that more than a brief recapitulation here of the basic facts would be redundant.

Approximately 85 per cent of individuals of the white race carry in or on their red blood cells an antigen known as the Rh factor—they are "Rh-positive." The remaining 15 per cent are Rh-negative in that they do not possess this antigen. When Rh-positive red blood cells are introduced into the tissues or blood stream of an Rh-negative individual, the serum of the latter may develop Rh antibodies which have the power of agglutinating and/or hemolyzing Rh-positive red blood cells. This antibody-producing ability varies considerably among Rh-negative individuals, sensitivity to the antigen being high in some and quite low in others. Such iso-immunization or sensitization, once established, may persist for long periods of time.

This mechanism explains many of the transfusion reactions which occur between apparently compatible bloods; the latter are compatible in the A, B, O group system but not for the Rh characteristic. Such transfusion reactions occur in individuals who have been immunized to Rh-positive red blood cells by previous transfusion, multiple transfusions, intramuscular injection of blood, or by iso-immunization attendant on gestation. The latter is of especial interest to the obstetrician.

The possession of the Rh factor by the red cells of an individual is a matter of inheritance. The characteristic is brought about by two allelic genes represented as Rh (positive) and rh (negative), the former being a dominant gene in the Mendelian sense. Thus an Rh-positive phenotype may be either homozygous (RhRh) or heterozygous (Rhrh), whereas an Rh-negative phenotype can only be homozygous (rhrh). It is apparent, then that any mating involving a homozygous Rh-positive husband or wife can only give rise to an Rh-positive phenotype offspring. Where both husband and wife are Rh-negative the child must also be Rh-negative.

The obstetrician is especially concerned with those matings in which the wife is Rh-negative and the husband Rh-positive, for if the latter be homozygous an Rh-positive child will always result, while if he be heterozygous there is a 50 per cent chance of producing an Rh-positive child. It is when this type of Rh mismatching occurs—an Rh-positive child borne by an Rh-negative mother—that serious obstetrical problems are most likely to eventuate. The chance that such a mating will result in an Rh-positive child is about 70 per cent.

Under these circumstances the presence of the Rh-positive child in utero may lead to iso-immunization of the mother. The basic mechanism responsible for this effect is probably the introduction of fetal red blood cells into the maternal circulation, but the factors controlling its occurrence and extent remain to be clarified. A defect in the placental barrier must be postulated; and it may be that the not uncommon "deportation of villi" satisfies this requirement. The known variability of sensitivity to Rh antigen action undoubtedly plays some part in the maternal reaction to fetal red blood cells. In any event, many Rh-negative mothers who carry Rh-positive pregnancies show no evidence of Rh antibody formation, whereas others develop a rapidly rising titer.

Whatever the regulatory factors may be, whenever an Rh-positive fetus immunizes an Rh-negative mother the maternal antibodies are passed through the placenta to the fetus with varying detrimental results to it. There is thus produced an agglutination and hemolysis of the fetal Rh-positive red blood cells, resulting secondarily in progressive anemia, liver damage, splenomegaly, hypoproteinemia, jaundice, edema, extramedullary erythropoiesis, placental changes, and fetal hypoxemia; in short, all the signs of erythroblastosis fetalis. This is, indeed, the generally accepted pathogenesis of the major percentage of cases of this disease—perhaps better termed hemolytic disease of the newborn.

This mechanism may function with varying speed in different Rh-negative mothers; rapid production of maternal antibodies with severe damage to the fetus may occur in the first pregnancy of one mother; iso-immunization in another mother may not become well enough established to be appreciably harmful to the fetus until the second, third, or fourth pregnancy.

Transfusion of incompatible Rh blood, however, constitutes a more direct method of establishing Rh antibodies in an Rh-negative mother—without the occurrence, be it noted, of any transfusion reaction. Giving such a woman Rh-positive blood—at any time prior to or during the childbearing age—may establish such a potentially high level of Rh antibodies that the Rh-positive infant of a subsequent pregnancy, subject to the hemolyzing and agglutinating action, may manifest hemolytic disease of the newborn.

The foregoing summary of the role of the Rh factor in the etiology of hemolytic disease of the newborn (erythroblastosis fetalis) is, of course, an oversimplification, for many cases of the disease—to be discussed presently—cannot be accounted for on this basis. Perhaps a scrutiny of clinical cases will point out more clearly the areas of the Rh-factor problem where our knowledge is incomplete.

INCIDENCE OF HEMOLYTIC DISEASE OF THE NEWBORN

In its full-blown manifestation erythroblastosis fetalis presents an unmistakable clinical picture,

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From the Division of Gynecology and Obstetrics and the Sub-division of Preventive Medicine, University of California Medical School.

whether in the icterus gravis or hydrops fetalis variety; and even lesser degrees of hemolytic disease of the newborn leave little doubt as to the diagnosis. But a moderate number of newborn infants in whom a definite diagnosis of erythroblastosis cannot be made show, nevertheless, one or more of the physical signs and laboratory findings associated with the disease. The incidence of such offspring in matings involving mixed Rh types has been such as to lead us to feel that we may be dealing with subclinical manifestations of hemolytic disease of the newborn. (Indeed, the occurrence of such cases constitutes one reason for preferring the broader term "hemolytic disease of the newborn" to the narrower one "erythroblastosis fetalis.")

Thus, the occurrence of such conditions as enlarged liver, enlarged spleen, nucleated red blood cells in excess of 5 per 100 white blood cells, icterus, bleeding tendencies, anemias, golden yellow amniotic fluid, hydrocephalus, and edema may well be evidences of a mild trauma to the fetus resulting from Rh iso-immunization. From the series of cases to be presented here we have selected 20 which seem to warrant consideration from this point of view. The clinical bases for this selection are presented in Table No. 1. In considering the obstetrical aspects of the Rh factor it is well to bear in mind that these subclinical

TABLE 1.—*Findings in Infants Judged to Show Subclinical Manifestations of Hemolytic Disease of the Newborn*
(20 cases)

Rh POSITIVE INFANTS:

* Case No. 1: Icterus, enlarged spleen, NRBCs—4%
No. 2: Persistently enlarged spleen
No. 3: Persistently enlarged liver and spleen
No. 4: NRBCs—14%
No. 5: Persistently enlarged liver and spleen
No. 6: Yellow vernix, enlarged liver and spleen, NRBCs—12%
* No. 7: Prematurity, icterus, anemia, enlarged liver, NRBCs—9%
No. 8: Icterus, enlarged liver and spleen, NRBCs—10%
No. 9: Persistently enlarged liver and spleen, Melena
* No. 10: Edema, icterus, NRBCs—4%
No. 11: Enlarged spleen, NRBCs—6%
No. 12: Enlarged liver, icterus, petechiae, NRBCs—4.5%
No. 13: Yellow amniotic fluid, enlarged liver
No. 14: Prematurity, enlarged spleen, hydrocephalus, NRBCs—1%

Rh NEGATIVE INFANTS:

No. 15: Icterus, enlarged liver and spleen, NRBCs—5% } Twins
No. 16: Icterus, enlarged liver, NRBCs—4% }
No. 17: Enlarged liver, NRBCs—5%
No. 18: Enlarged liver, persistent edema
* No. 19: Icterus, anemia, enlarged spleen, NRBCs—40%
No. 20: Icterus, NRBCs—8%

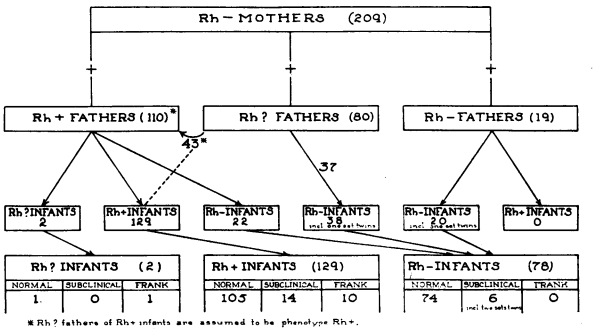
* Cases in which a diagnosis of hemolytic disease of the newborn was entertained but not definitely made.

("NRBCs—10%" signifies "nucleated" red blood cells—10 per hundred WBCs.)

cases may well represent a group of infants with an impaired but not hopeless survival prognosis, a group which will be the most susceptible to salvage through clinical alertness and skillful therapy.

The very nature of Rh iso-immunization indicates that from a practical clinical viewpoint the pregnancies of Rh-negative mothers will require the principal attention. The illustrative material here presented consists of 209 such pregnancies resulting in the birth of 211 infants (two sets of twins) in the Division of Obstetrics and Gynecology of the University of California Hospital. Table No. 2 presents the data concerning them with regard to: Rh factors involved in each mat-

TABLE NO.2.
INFANTS BORN TO Rh NEGATIVE MOTHERS.
Occurrence of frank and subclinical manifestations of Hemolytic Disease of the Newborn.
Material from U.C.H. Obstetrical Department Oct. 1943-July, 1946



* Rh ? fathers of Rh + infants are assumed to be phenotype Rh +.

ing, Rh status of the infants, and presence or absence of hemolytic disease of the newborn.

Table No. 3 presents the incidence of hemolytic disease of the newborn for the 209 pregnancies. There were 11 frankly erythroblastotic babies, an incidence of 5 per cent. Of these 11 infants only two survived, a mortality of 82 per cent. Twenty infants of these pregnancies showed subclinical manifestations of hemolytic disease of the newborn, an incidence of 10 per cent. All of these 20

TABLE NO.3.
INCIDENCE OF HEMOLYTIC DISEASE OF THE NEWBORN IN INFANTS OF Rh NEGATIVE MOTHERS.
(211 INFANTS)

TOTAL INCIDENCE	FRANK—5.2% (11)	14.7%
	SUBCLINICAL—9.5% (20)	
INCIDENCE IN Rh + INFANTS	FRANK—5.2% (11)	11.8%
	SUBCLINICAL—6.6% (14)	
INCIDENCE IN Rh – INFANTS	FRANK—0% (0)	2.9%
	SUBCLINICAL—2.9% (6)	

infants survived the neonatal period. Fifteen per cent, then, of infants of Rh-negative mothers suffered from the effects of iso-immunization, and for these 31 infants the mortality was 29 per cent.

RELATION OF HEMOLYTIC DISEASE OF THE NEWBORN TO PARITY

All investigators have emphasized that increasing parity subjects successive Rh-positive infants to increasing risk. But there has been, perhaps, an overemphasis on the degree of safety enjoyed by the child of a primigravidous mother. While our series of cases is too small to permit full analysis with regard to parity of the mothers, an inspection of it from this viewpoint is illuminating. Of the 211 infants 92, or 44 per cent, were delivered of primigravidae. Of the 31 cases of

hemolytic disease of the newborn 12, or 39 per cent, were infants of primigravidous pregnancies, and of this number 2 were cases of frank erythroblastosis fetalis. It is apparent, then, that when a mother is Rh-negative obstetrical vigilance cannot be relaxed appreciably simply because she is carrying her first pregnancy.

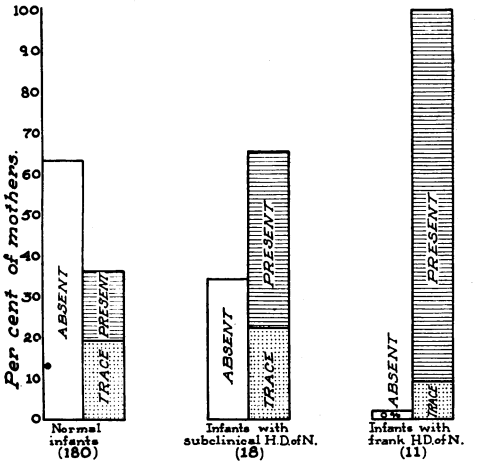
ANTEPARTUM PREDICTION OF HEMOLYTIC DISEASE OF THE NEWBORN

What observations shall this vigilance include? Fortunately, the availability of fairly simple and satisfactory titration methods,[15] not only for Rh typing but also for Rh antibodies, provides an opportunity to be forewarned prior to delivery of an infant with hemolytic disease of the newborn. Rh typing of all pregnant mothers at once separates them into an Rh-positive group, in which the likelihood of fetal affliction is extremely small, and an Rh-negative group in which its incidence is high. When, in the latter group, the father is Rh-positive, continued attempts must be made to discern the presence of the disease in the intrauterine fetus.

This is best—though still unsatisfactorily—accomplished at present by means of repeated antepartum determinations of maternal Rh antibody titer. While the interpretation of titer levels is not yet clear, most workers agree that the appearance of any detectable Rh antibody in the maternal serum should warn the obstetrician that the intrauterine fetus is probably being subjected to hemolytic disease damage.

Fig. 1 presents a graphic representation of the correlation, for our series of cases, of the clinical status of infants of Rh-negative mothers and

RELATION OF MATERNAL ANTI-Rh ANTIBODIES TO THE CLINICAL STATUS OF INFANTS OF Rh NEGATIVE MOTHERS.



Percent of mothers of each group of infants showing presence or absence of anti-Rh antibodies at any time during pregnancy or puerperium. (Twins considered as one infant.)
(Trace of antibody equals less than 1-plus titer.)

Fig. 1.

the presence or absence of maternal anti-Rh titer at any time during pregnancy or the puerperium. In the 209 pregnancies titers were recorded as absent, trace, 1-, 2-, 3-, and 4-plus; for analysis here they have been consolidated to absent, trace, and present.

One hundred per cent of mothers of frankly erythroblastotic infants showed the presence of a trace or more of Rh antibodies. Sixty-six per cent of the mothers of infants with subclinical hemolytic disease of the newborn showed a trace or more—though 34 per cent of such mothers showed no titer at any time even though their infants apparently suffered from some degree of the disease. Sixty-four per cent of the mothers of clinically normal infants showed no Rh antibody. Note, however, that 36 per cent of such mothers did develop antibodies even though no evidence of iso-immunization damage could be clinically observed in their infants. The cause of such antibody development is at present unknown—or, from the opposite viewpoint, the reason why the babies are protected from damage is unknown.

From a clinical point of view we can only conclude that while the antepartum occurrence of maternal Rh antibodies leads to an increased expectancy of delivery of a damaged infant, it does not necessarily predict such an outcome. On the other hand, absence of maternal Rh antibodies does not necessarily mean that the infant will escape all manifestations of hemolytic disease of the newborn—though in the small series reported here frank erythroblastosis was invariably associated with the development of maternal Rh antibodies (only a trace in one case).

The recent discovery by Wiener[15,16] of the so-called "blocking antibody" has complicated the situation. While the exact nature of this antibody is as yet undetermined, it is known to act in such a way as to spoil or "block" the usual agglutination test for Rh antibodies. Thus, the presence of blocking antibodies in maternal serum may serve to obscure the presence of Rh agglutinins if only the simple test for the latter is run. Fortunately, the blocking antibodies may be titrated separately;[16] and it is likely that both tests will be required for all antepartum mothers where Rh immunization is suspected if we are to predict with any accuracy the occurrence of hemolytic disease of the newborn. The findings represented by Fig. 1, for example, are probably explained to some extent by the blocking antibody factor, which was not taken into account in this analysis.

Recently, however, Page, Hunt, and Lucia,[9] testing antepartum maternal sera for both Rh agglutinins and blocking antibodies, have given further insight into the significance of these antepartum titrations. Their findings indicate that while the height of the titer may tell us something about the likelihood of hemolytic disease of the newborn, much more indicative is the *length of time* before delivery that these antibodies are present in maternal serum. The graphic chart of Fig. 2 was constructed, with the permission of the authors, from the data of Page, Hunt and Lucia's paper. (Their clinical criteria for subclinical manifestations of hemolytic disease of the newborn approximate our own.)

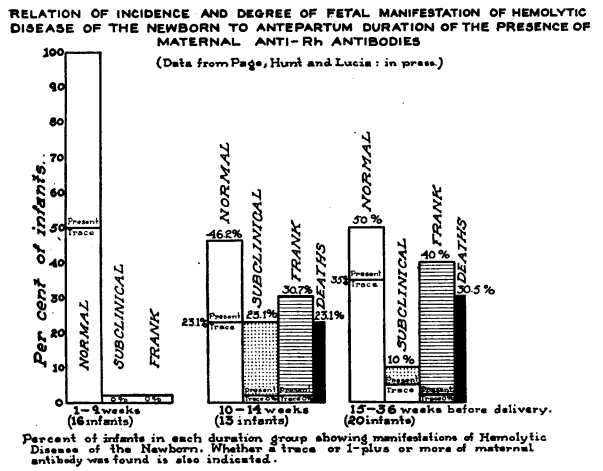


Fig. 2.

While their series of cases is small, it is highly suggestive of certain conclusions. When either antibody appeared in the maternal serum only 1 to 9 weeks before delivery, 100 per cent of the delivered infants were clinically normal. When it appeared 10 to 14 weeks before delivery, 54 per cent of the delivered infants showed some evidence of hemolytic disease of the newborn. When it appeared 15 to 36 weeks before delivery, 50 per cent of infants showed the disease.

More important than incidence of the disease is the fact that the severity of its manifestation paralleled even more closely the antepartum duration of maternal titer. Thus, in the 1- to 9-week group there was no frank erythroblastosis fetalis; in the 10- to 14-week group 31 per cent of the infants had frank erythroblastosis fetalis, and the mortality for the group was 23 per cent; in the 15- to 36-week group 40 per cent of the infants were frankly erythroblastotic, and the mortality for the group was 31 per cent.

The clinical implications of these findings are so clear-cut that reference will be made to them again in the discussion of prophylaxis and treatment of hemolytic disease of the newborn.

HEMOLYTIC DISEASE OF THE NEWBORN FROM CAUSES OTHER THAN Rh IMMUNIZATION

Table No. 3 shows an incidence of 3 per cent of hemolytic disease of the newborn occurring in Rh-negative infants, all of the 6 cases thus represented being subclinical manifestations. But that frank erythroblastosis fetalis may occur under similar circumstances is illustrated by the case of a private patient not included in our series. This patient was a 21-year-old primigravida whose blood study revealed a negative Kahn and Kolmer, Group O, Rh-negative. The delivered infant, Group A, Rh-negative, had frank erythroblastosis fetalis but survived the neonatal period. Postpartum study of the maternal serum showed no evidence of Rh antibodies but the anti-A titer fluctuated between 1/128 and 1/1024. Boorman, Dodd and Mollison[1] reported two cases of clinical erythroblastosis fetalis in infants whose bloods were both Group B, Rh-positive while those of the mothers were Group O, Rh-positive. The maternal anti-B titers were 1/3200 and 1/8,000,000 respectively. LaVake[6] reported a similar case. Polayes[10] reported two cases of Group O, Rh-positive mothers who bore Group A, Rh-positive infants; both infants were frankly erythroblastotic. The maternal anti-A titers were 1/700 and 1/750 respectively.

It is clear then that iso-immunization by antigens other than the Rh antigen may, through a similar mechanism, produce hemolytic disease of the newborn. Indeed, it is likely that Rh subgroup reactions may account for a few cases, eight such sub-groups having been established.[15] The part that M, N, and P sub-groups may play has not yet been delineated.

The existence of an Hr antigen has also been established,[7,8,13] so called because it is present in the blood of Rh-negative individuals. While it appears to have been the etiological factor in a few cases of hemolytic disease of the newborn, its importance has not yet been clarified. At present, however, titrations of it are thought to be of some value in determining whether an Rh-positive individual is homozygous or heterozygous, a matter of considerable importance in predicting the status of future infants of Rh-positive father-Rh-negative mother matings.

On the whole, however, obstetricians will be well advised to bear in mind that hemolytic disease of the newborn may occur unexpectedly, though very rarely, in infants of matings where the bloods are supposedly compatible.

PROPHYLAXIS OF HEMOLYTIC DISEASE OF THE NEWBORN

Protection of prospective mothers from iso-immunization, insofar as this is possible, is, of course, of prime importance in preventing the occurrence of hemolytic disease of the newborn. Any woman before or during the childbearing age for whom blood transfusion is contemplated should have Rh typing as well as the routine cross-matching procedures in order to eliminate the possibility of introducing Rh-positive blood into an Rh-negative blood stream. Obstetricians and pediatricians cling to the habit of giving blood intramuscularly to newborn infants for various purposes. Whether an iso-immunization to the Rh factor thus produced in a female child would persist long enough to increase the fetal hazard in a subsequent pregnancy has not yet been established; but until enough years pass to clarify this point it might be advisable to avoid this time-honored but dubious procedure.

That all pregnant women should routinely have Rh typing is self-evident. The husbands of those who are Rh-negative should be similarly studied in order to prepare for and warn the prospective parents of the possible eventualities. While the present serological methods for determining whether an Rh-positive father is homozygous or

heterozygous are still in the experimental stage, we may reasonably expect them to be developed to a degree of dependability which will make the prediction of the chances for the occurrence of an Rh-positive child much more certain. For the present, careful scrutiny of the previous obstetrical history in multigravidae often constitutes the only mode of approach to this information.

Dissemination of information about the Rh factor and erythroblastosis through lay publication channels has resulted in the obstetrician being increasingly confronted by requests for advice from worried prospective parents—especially when the latter have discovered that they are Rh incompatible. Even nulliparous wives now express doubts about undertaking pregnancy at all in the face of such incompatibility.

Such patients may be reassured by the fact that the likelihood of a primigravidous mother bearing a frankly erythroblastotic child is not great, and that even if one is borne its survival chances are reasonably good. Potter and Wilson,[12] reporting over 100 erythroblastotic infants, found 100 per cent survival in those borne by primigravidae —though the number of such infants is not given. (Indeed, this absence of mortality for an admittedly lethal disease leads one to wonder about their criteria for diagnosis.) On the other hand, the likelihood that an Rh-negative mother with an Rh-positive husband will bear a frankly erythroblastotic child is not as negligible as some authors have suggested. Even in our small series two such cases were encountered, neither one of which was the result of previous transfusion, and only one of which survived. The primigravida, however, runs such a small risk of bearing a stillborn or seriously injured infant that when she allows fears about erythroblastosis to upset her, emphasis should be placed on the probability of a happy fetal outcome.

The outlook for the later pregnancies of the Rh-incompatible couple is less hopeful though not by any means grave. If, in previous pregnancies, no serological or fetal clinical evidence of maternal iso-immunization has been encountered, the risk to the child is not much greater than it was in previous pregnancies, and the patient may be reassured on this basis.

Once maternal iso-immunization has been established, however, the picture changes abruptly. In subsequent pregnancies the likelihood of an unfortunate fetal outcome greatly and progressively increases—especially if the father be a homozygous Rh-positive. Guidance of the iso-immunized mother constitutes a difficult problem. Our knowledge of the factors involved in the production of hemolytic disease of the newborn is still too incomplete to permit of any definitive decision regarding advice to mothers under such circumstances. Cases will require individualization based on serological study and previous obstetrical history. But with increasing frequency three questions present themselves: that of the justification for sterilization, the justification for therapeutic abortion, and the propriety of artificial insemination with semen from an Rh-negative donor. The final answers become a matter for individual decision, to the ease of which further knowledge will undoubtedly contribute.

The study of anteparum anti-Rh and blocking antibody titers, however, offers one avenue of attack in the prophylaxis of hemolytic disease of the newborn. Dependence upon the level of titer alone would seem ill-advised at present. Uncertainty still exists regarding its significance. A rising titer may indicate increasing damage to the fetus or it may not. Possibly a rising titer followed by a fall may point to more rapid absorption of maternal Rh antibodies by the fetus with consequent increasing damage.[4]

The work of Page, Hunt, and Lucia, however, suggests very strongly that the antepartum duration of detectable maternal anti-Rh (or blocking antibody) titer may serve as a measure of the severity of hemolytic disease in the intrauterine fetus. Present opinion is divided on the value of premature interruption of pregnancy for the purpose of averting serious manifestations of the disease in the newborn. It is difficult to decide between the increasing hazards which go with increasing prematurity and those to which a fetus is subject while it remains in an environment where Rh antibodies have access to its blood.

On the other hand, if the findings of Page, Hunt and Lucia are confirmed by larger series it would appear that increasing time spent by a fetus in such a detrimental uterine environment—no matter what the type and concentration of maternal Rh antibodies—is more damaging than we had suspected. The dividing line between serious and subclinical damage would seem to fall at approximately 10 weeks antepartum. For an Rh-negative mother, then, who first evidences anti-Rh titer *less than 10 weeks* before term it would seem advisable to allow spontaneous onset of labor unless the pregnancy carries beyond the expected date. On the other hand, in a mother who first shows anti-Rh titer *more than 14 weeks* before term, the probability that severe fetal damage will already be present by the time premature induction of labor is feasible is very great. It seems so great that the added risk to the fetus of prematurity and the added hazards to the mother of procedures for premature interruption of pregnancy would make unjustifiable the use of the latter. Those cases in which maternal Rh antibodies appear *between 10 and 14 weeks* before the expected date of confinement would require, in deciding upon premature termination of pregnancy, a nicety of judgment to which, unfortunately, clinical observation and laboratory findings can contribute little further information in the present state of our knowledge.

When the disease is suspected before parturition, for one or another of the reasons we have mentioned, special care should be exercised with

regard to analgesia and anesthesia during labor and delivery. No means should be practiced which reduces the oxygen carried by maternal blood, since the fetus, already struggling to overcome an impaired oxygen-carrying capacity of its blood, will thus be further embarrassed by hypoxemia.

All infants born to Rh-negative mothers should have immediate study of their blood: hemoglobin determination, red blood cell count, count of nucleated red blood cells, Rh determination, and A, B, O blood-group determination. The counts should be repeated at frequent intervals until the possibility of a progressive anemia is ruled out, and careful observation should be maintained for clinical evidence of the disease. In this connection it is important to bear in mind that one of the striking characteristics of hemolytic disease of the newborn is its tendency to manifest itself some days or weeks after delivery. Thus, an infant, apparently normal at birth, may suddenly develop a profound anemia which may go unrecognized if clinical and hematological alertness are relaxed. Moreover, almost all erythroblastotic infants tend to go downhill with increasing speed, and the resulting pathological changes may become irreversible unless treatment is prompt.

Transfusion is the principal method of treatment at the present time. In general, a red blood cell count of three million or less is an indication for it, while a count of two million or less indicates a very poor prognosis and is an urgent indication for transfusion. Routine transfusion, however, of all erythroblastotic babies at birth may subject some of them to unnecessary trauma. Those few cases which present, at the outset, normal newborn hemoglobin levels and red cell counts may suffer more damage from having extra blood crowded into their circulations than from the disease itself. It is advisable in such cases to postpone transfusion until blood studies indicate an actual need for it.

Where Rh incompatibility appears to be the etiology of hemolytic disease of the newborn almost all workers agree that Rh-negative blood should be given. If there is the slightest suspicion of other blood-group incompatibility, Group O blood should be used. Wiener[15] states that when Rh-negative blood other than that of the mother is not available, her blood may be used for transfusion of the infant if the red cells are properly washed free of plasma and resuspended in compatible plasma. It might be safer to use maternal blood in this way only when it is Group O or group-compatible with that of the child.

Erythroblastotic infants should not be permitted to nurse, inasmuch as Rh antibodies are excreted in the mother's milk.

Whereas in the icterus gravis variety of hemolytic disease of the newborn replacement of blood is the principal rationale for transfusion, in the more deadly hydrops fetalis variety the added problem of marked hypoproteinemia is met. While transfusion combats this to some extent, speculation may be entertained as to whether additional protein, or protein alone in those cases without marked anemia—plasma, for example—might be of value.

Many erythroblastotic infants manifest not only the anemia but also a bleeding tendency. The cause of the latter is unknown, though defective utilization of Vitamin K secondary to liver damage has been called in question. In general these infants do not lack Vitamin K. While its administration probably serves no useful purpose, it certainly can do no harm.

Oxygen therapy, particularly for the icteric and anemic group of infants, has proved to be of some value, especially if the red blood cell count is very low. Whether oxygen therapy to the mother during labor and delivery appreciably aids the fetus remains undecided.

As is evident from the mortality rates, our present treatment of hemolytic disease of the newborn leaves much to be desired. As would be expected from the present state of our knowledge, treatment is actually directed more at symptoms and signs of the disease than it is at causative pathological processes. One gains the impression, for example, that these infants die "liver deaths," that liver damage of various types plays a large part in the clinical picture. Yet at present there are no available treatment methods specifically designed to protect the fetal liver antepartum or to hasten its healing postpartum. Further work along these lines may well reward us with more adequate therapeutic procedures.

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